## REMARKS

### I. General

Claims 1-50 are pending in the instant application.

Applicant thanks the Examiner for considering Applicant's Information Disclosure Statement.

### II. Claim rejections under 35 U.S.C. § 102

A. U.S. Patent No. 5,271,946 to Hettche et al.

Claims 1-5, 9-20, 24-30, 34-42, and 45-46 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hettche et al., U.S. Patent No. 5,271,946 (hereinafter "the '946 patent"). (Office Action, p. 2). Applicant respectfully traverses this rejection.

The Office Action states:

> The '946 patent teaches a sustained release pharmaceutical dosage form comprising a multiplicity of particles coated with a sustained release polymer (abstract, col. 3, lin. 10-15). The dosage form can be administered via a suspension of the coated particles (col. 3, lin. 22-26, col. 3, lin. 58-61). The core particle comprising the active agent is coated with a polymer solution comprising alkylcellulose polymers that can be both hydrophilic and hydrophobic such as ethylcellulose and hydroxypropylcellulose (col. 3, lin. 65-col. 4, lin. 35). The coated cores are further coated with semi-permeable coating comprising alkylcellulose polymers (col. 4, lin. 26-45). The second coating is semi-porous comprising porous and non-porous areas (col. 5, lin. 65 - col. 6, lin. 28).
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> (Office Action, p. 2).

An object of the '946 patent is to "provide a pharmaceutical composition containing the active substance azelastine which significantly reduces or completely eliminates the sedative effect of azelastine and which has a more acceptable taste." (col. 2, lines 13-17). The '946 patent achieves this object by providing pharmaceutical compositions for controlled release of

azelastine. (col. 2, lines 20-22). However, these pharmaceutical compositions are very different from the claimed pharmaceutical preparations of the instant application. The '946 patent describes its compositions as follows:

> The composition contains conventional auxiliary substances and additives and a sustained release component which is characterized in that the active substance, azelastine, or its physiologically acceptable salts, are released in a controlled manner. A dosage unit of the composition contains 0.001 to 800 parts by weight of sustained release components are present together with each 1 part by weight of azelastine calculated as base.
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> (col. 2, lines 22-30).

Thus, the compositions of the '946 patent are mixtures of "conventional auxiliary substances and additives and a sustained release component." The presently claimed preparation comprises core particles comprising the active pharmaceutical ingredient and a polymeric coating on those core particles.

The composition of the '946 patent is further illustrated by the process for its preparation:

> The present invention also provides a process for the preparation of a drug formulation with controlled release of the active substance by incorporation of an active substance in conventional auxiliary and ancillary substances and a sustained release component which is characterized in that azelastine or its physiologically acceptable salts are used as the active substance to be released in a controlled manner in the ratio of 1 part by weight of azelastine, calculated as base, to 0.001 to 800 parts by weight of the sustained release component whereby the azelastine is released at a rate of 0.05 to 5 mg per hour.
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> (col. 2, lines 42-54, emphasis added).

Thus, the "formulation with controlled release of the active substance" is a mixture of the "active substance in conventional auxiliary and ancillary substances" and "a sustained release component." The instantly claimed preparation is not a mixture but, rather, comprises a multiplicity of coated microparticles.

The '946 patent describes the coating of "active ingredient particles, granulate or pellet grains or azelastine-containing tablets." (col. 3, lines 63-65). The '946 patent makes no mention of coating of microparticles, as instantly claimed. The "particles" referred to are in the context of compositions such as pellet grains and tablets – compositions that are much larger than the instantly claimed microparticles. Furthermore, there is no teaching that the substances used to coat the active ingredient particles, granulate or pellet grains, or tablets must be permeable to the active ingredient. Such permeability is a limitation of the preparations of the instant claims that is not found in the '946 patent. Without such a teaching in the '946 patent, a person of ordinary skill in the art would not understand which polymers to use with which active pharmaceutical ingredients to arrive at the sustained-release pharmaceutical preparations of the instant claims.

Moreover, the '946 patent does not teach that the active pharmaceutical ingredient forms a saturated solution within the microparticles, as presently claimed. The permeability of the polymeric coating and the ability of the active pharmaceutical ingredient to form a saturated solution within the coated microparticles are limitations of the presently claimed pharmaceutical preparations that are not found in the '946 patent.

The differences between the '946 patent and the claims of the instant application are further illustrated by the examples in the '946 patent. For example, Example 1 of the '946 patent describes preparation of the mixed formulation as follows:

> 100 g of azelastine hydrochloride are mixed with 960 g of hydroxypropyl methyl cellulose [viscosity of a 2% aqueous solution: 4000 cP (commercial product: e.g. Methocel K4M Premium)], 1320 g of spray-dried lactose and 20 g of magnesium stearate and the mixture pressed into tablets weighing 120 mg, having a diameter of 6 mm and a radius of curvature of 6 mm.
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> In conjunction therewith the tablets may be provided in a conventional procedure with a gastric juice-soluble or gastric juice permeable or gastric juice-resistant film coating.

> To produce a gastric juice-resistant coating, 1000 g of tablets are sprayed with about 1000 g of the following suspension, for example in a coating drum: ...
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> (col. 12, lines 40-53, emphasis added).

The active pharmaceutical ingredient is mixed, not coated, with the sustained release component (i.e., hydroxypropyl methyl cellulose), as well as other ingredients. Thus, the sustained release component does not form a permeable coating. The only coating that is provided in this Example is not added to cause the sustained-release of the active pharmaceutical ingredient, but to be either "gastric juice-soluble or gastric juice permeable or gastric juice-resistant." Such coatings relate to absorption of the active pharmaceutical ingredient in the stomach or the intestine, not to the sustained-release of a active pharmaceutical ingredient administered parenterally.

By mixing, rather than coating, the active pharmaceutical ingredient with a sustained release component, by failing to teach a polymeric coating that is permeable to the active pharmaceutical ingredient, and by failing to teach that the active pharmaceutical ingredient forms a saturated solution within the microparticle, the '946 patent does not teach the instantly claimed sustained-release preparations. This is illustrated in Example 9 of the '946 patent. As can be seen from the data in column 16, the release of the azelastine was highly non-linear. Such release does not even approximate the pseudo-zero-order release that can be obtained with the claimed preparations of the instant application.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); Patent and Trademark Office, MANUAL OF PATENT EXAMINING PROCEDURE § 2131 (8th ed. July 2008 Revision). Because the '946 patent does not teach microparticles that comprise coated core particles wherein the polymeric coating is permeable to the active pharmaceutical ingredient and the active pharmaceutical ingredient

forms a saturated solution within the coated microparticles, the '946 patent does not anticipate the amended claims.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1-5, 9-20, 24-30, 34-42, and 45-46 under 35 U.S.C. § 102(b) based on the '946 patent be withdrawn.

B. U.S. Patent No. 5,133,974 to Paradissis et al.

Claims 1-4, 6, 9-19, 24-25, 27-31, 34-42, and 44-45 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Paradissis et al., U.S. Patent No. 5,133,974 (hereinafter "the '974 patent"). (Office Action, p.4). Applicant respectfully traverses this rejection.

The Office Action states that the '974 patent teaches:

> a sustained release formulation comprising coated core particles comprising a drug and a second coating applied to the core, wherein the coated particles exhibit a zero order release of the drug (abstract). The core particle comprises a drug coated to a sugar sphere (col. 4, lin. 12-20). The drug coated sphere is sprayed with a solution comprising a first binding polymer including cellulose, vinyl and acrylic based polymers (col. 5, lin. 40-45). These polymers include hydrophilic polymers such as hydroxypropylmethylcellulose of hydrophobic polymers such as ethylcellulose (Ibid.). The coated drug sphere is further coated with second polymer comprising a film forming agent that forms a sustained release particle (col. 6, lin. 67-col. 7, lin. 10). These film forming agents include cellulose derivates (Ibid.). The second polymer can comprise pore-forming agents present in the coating layer (col. 7, lin. 10-15). These pore-forming agents comprise 25% of the layer, meaning there are portions of the layer that are porous and non porous. These particles once coated have a size of at least 250 microns (col. 7, lin. 22).
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> (Office Action, p. 4).

The '974 patent teaches a pharmaceutical formulation quite different from the claimed pharmaceutical preparation. As acknowledged by the Examiner, "the core particles comprising a

drug are coated to a sugar sphere." (Office Action, p. 4). This is the "immediate release particle." ('974 patent, col. 4, lines 12-20). "The immediate release particle core additionally contains an inert spherical substrate particle which aids in the diffusion/release of the drug from the formulation." (col. 5, lines 23-26). "The drug adheres to the inert spherical substrate particle through a binding agent which is preferably applied by a suitable solvent. (col. 5, lines 38-40).

The immediate-release particle of the '974 patent, by definition, does not disclose the claimed sustained-release preparations. The '974 patent also does not disclose that the active pharmaceutical ingredient "forms a saturated solution within said coated microparticles after said administration," as presently claimed. The ability of the active pharmaceutical ingredient to form this saturated solution is a limitation of the claimed sustained-release formulation. Furthermore, the '974 patent does not disclose that the binder is "permeable to said active pharmaceutical ingredient," as presently claimed with respect to the first polymeric coating. Thus, the '974 patent fails to teach these two elements of the instant claims.

To obtain the extended release particles, the '974 patent coats the immediate release particles with a plasticizer and a film forming material as part of its dissolution modifying system. (col. 6, line 19 – col. 7, line 10). Thus, the extended release particles of the '974 patent comprise active pharmaceutical ingredient with a binder to adhere the active pharmaceutical ingredient to an inert spherical carrier that is then coated with a plasticizer and a film forming material. This is starkly different from the presently claimed sustained-release preparations, which comprise core particles comprising an active pharmaceutical ingredient and a polymeric coating on those core particles, without the addition of a second film forming agent or a plasticizer.

The '974 patent also discloses that its formulations are matrices. For example, the '974 patent states:

> In particular it is essential to use starting components of drug and inert carriers which have mesh sizes greater than 200 mesh. Such

> sizes aid in offering various advantages. First, they assist in making hard granules which improves the binding characteristics of the matrix.
>
> (col. 7, lines 30-35).

The '974 patent also states:

> By employing the formulations of the invention, one is able to achieve an extended release system which is a dynamic system composed of wetting, hydrating and dissolution components. At the same time, other soluble materials or drugs will also wet, dissolve and diffuse out of the matrix while insoluble materials will be held in place until the surrounding encapsulation layer erodes or dissolves away.
>
> (col. 7, lines 42-49).

The pharmaceutical preparation of the claims of the instant application are not a matrix, but comprise core particles comprising active pharmaceutical ingredient and a polymeric coating on those core particles. The difference between the claimed preparations and a matrix is described, for example, in the specification at ¶ [0054], which states, in pertinent part:

> [0054] If the active pharmaceutical ingredient and the first polymer-forming solution are both hydrophobic or hydrophilic, the core particle may partially or completely dissolve in the polymer-forming solution, resulting in microparticles in which the active pharmaceutical ingredient is interspersed or embedded in a matrix of the polymer as opposed to being coated by the polymer.

The specification describes the advantages of the present invention over the matrices formed in the prior art at ¶¶ [0059] and [0063], which read as follows:

> [0059] Moreover, many active pharmaceutical ingredients and many commonly-used polymer-forming solutions are hydrophobic in nature. As a result, core particles of such active pharmaceutical ingredients tend to dissolve in many commonly-used polymer-forming solutions if the solutions are applied directly, resulting in microparticles in which the active pharmaceutical ingredient is interspersed or embedded in a matrix of the polymer as opposed to

> being coated by the polymer. Depending upon the degree of dissolution, such microparticles may not exhibit pseudo-zero-order kinetics of release. Therefore, a first polymeric coating can be employed which is formed from a hydrophilic first polymer-forming solution in which the active pharmaceutical ingredient is substantially insoluble. A second polymeric coating formed from a hydrophobic second polymer-forming solution can then be employed without dissolving the active pharmaceutical ingredient. Conversely, for hydrophilic active pharmaceutical ingredients, a first polymeric coating can be formed from a hydrophobic first polymer-forming solution followed by a second polymeric coating formed from a hydrophilic second polymer-forming solution.
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> ...
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> [0063] In addition, in contrast to prior art sustained-release particle formulations, the core particles of the present invention constitute a substantially larger portion of the overall volume and weight of the coated microparticles and, conversely, the polymeric coating(s) constitute a substantially smaller portion. This is advantageous because the overall volume of microparticles which must be administered per unit weight of the active pharmaceutical ingredient is reduced relative to the prior art particles in which the active pharmaceutical ingredient is dissolved or interspersed in a relatively large volume and weight of polymeric matrix material which releases the active pharmaceutical ingredient as it degrades. This advantage arises from the different mechanism of action of the coated microparticles of the invention, in which a relatively thin polymeric coating can contain a relatively large core which contains a saturated solution of the active pharmaceutical ingredient and permits release by diffusion with pseudo-zero-order kinetics.

Thus, the pharmaceutical preparations of the claims of the instant application are not matrices.

In addition to requiring plasticizers and film forming materials, the '974 patent is also directed solely to pharmaceutical formulations for oral administration. When describing which drugs may be used in its formulations, the '974 patent states that a "wide variety of medicaments which are orally administered both in tablet, capsule and particulate form may be used to prepare particles according to this invention." (col. 4, lines 26-29; emphasis added). The '974 patent

also states that the "formulations of the invention are administered orally to mammals in suitable amounts to achieve the drug efficacy sought." (col. 9, lines 25-27). The '974 patent provides no teaching and makes no mention of parenteral administration.

As noted above "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); Patent and Trademark Office, MANUAL OF PATENT EXAMINING PROCEDURE § 2131 (8th ed. July 2008 Revision). Because the '974 patent teaches extended release particles for oral administration that comprise a matrix comprising an active pharmaceutical ingredient and a binder adhered to an inert spherical carrier that is then coated with a plasticizer and a film forming material, the '974 patent does not teach the claimed pharmaceutical preparation for sustained-release of an active pharmaceutical ingredient after parenteral administration.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1-4, 6, 9-19, 24-25, 27-31, 34-42, and 44-45 under 35 U.S.C. § 102(b) based on the '974 patent be withdrawn.

C. U.S. Patent No. 5,286,497 to Hendrickson et al.

Claims 1-4, 6, 9-12, 16-19, 24, 27, and 43 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hendrickson et al., U.S. Patent No. 5,286,497 (hereinafter "the '497 patent"). (Office Action, p. 5). Applicant respectfully traverses.

The Office Action states that the '497 patent teaches:

> a sustained release formulation comprising multiple coated beads that exhibit zero-order release of an active agent (abstract, Figures). The beads comprise a core bead that is formed from compression (col. 6, lin. 10-16). The core comprises the drug and

> comprises a binding solution coated to the drug in order to keep the drug in place (col. 5, lin. 20-25). The binder solution comprises cellulose, vinyl and acrylic based polymers (col. 5, lin. 25-35). The coated drug core is further coated with a second polymeric coating comprising an acrylic based polymer (col. 6, lin. 10-50). The coated beads have a size range from 354-595 microns (col. 4, lin. 50-55).
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> (Office Action, p. 5).

The '497 patent discloses that a "new diltiazem formulation has been discovered that will optimize blood levels of diltiazem over a 24 hour period by decreasing the variance between peak and trough levels of diltiazem. The formulation is a controlled release dosage form which exhibits an *in vitro* stair stepped release profile." (col. 2, lines 60-66). This stair-stepped release profile is also illustrated in the data shown in FIG. 1-3. Such a stair-stepped release profile is quite different from the pseudo-zero-order kinetics of the preparations of the instant claims. This is because the '497 patent discloses delayed release of diltiazem, not sustained-release. It is the sustained-release aspect of the instantly claimed pharmaceutical preparations that provides the pseudo-zero-order kinetics.

To achieve a "controlled" release dosage form, the '497 patent teaches a blend of rapid release diltiazem beads and delayed release diltiazem beads. (col. 3, lines 16-18). This difference between the '497 patent and the instant claims is further illustrated by the description of the diltiazem beads:

> Both the rapid release diltiazem beads and the delayed release diltiazem beads are comprised of two parts. The first part is a central core which contains the diltiazem or a pharmaceutically acceptable salt thereof in association with conventional excipients (diltiazem blend). The central core of the rapid release diltiazem beads and the delayed release diltiazem beads may be identical and preferably are.
>
> (col. 4, lines 26-33).

Thus, the delayed release beads comprise a central core comprising diltiazem. There is, however, no teaching that the delayed release beads comprise a permeable polymeric coating or that the active pharmaceutical ingredient forms a saturated solution within a microparticle.

Similar to the '974 patent, the '497 patent discloses only diltiazem formulations for oral administration. The '497 patent states:

> The blended diltiazem beads may be administered by a number of dosage forms known in the art. For example, they may be placed into soft or hard gelatin capsules. The blended beads may be admixed with a binder such as microystalline cellulose and compressed into tablets. Alternatively, they may be placed in a liquid immediately prior to administration and administered as a suspension. Methods for producing these various dosage forms are known to those skilled in the art.

The '497 patent provides no teaching and makes no mention of parenteral administration. This is quite different from the claimed preparations for sustained-release of an active pharmaceutical ingredient after parenteral administration.

As discussed above, the claims of the instant application are directed to a pharmaceutical preparation for sustained-release of an active pharmaceutical ingredient after parenteral administration, wherein the active pharmaceutical ingredient forms a saturated solution within the microparticles after the parenteral administration. There is no teaching in the '497 patent that polymeric coating is permeable to the active pharmaceutical ingredient, as presently claimed. Moreover, the '497 patent does not teach that the active pharmaceutical ingredient forms a saturated solution within the microparticles, as presently claimed.

As also discussed above, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); Patent and Trademark

Office, MANUAL OF PATENT EXAMINING PROCEDURE § 2131 (8th ed. July 2008 Revision). Because the '497 patent does not teach the claimed preparations, the '497 patent does not anticipate the amended claims.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1-4, 6, 9-12, 16-19, 24, 27, and 43 under 35 U.S.C. § 102(b) based on the '497 patent be withdrawn.

**III. Claim Rejections under 35 U.S.C. § 103**

A. U.S. Patent No. 5,133,974 to Paradissis et al.

Claims 1, 6-8, and 31-33 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the '974 patent to Paradissis. (Office Action, p. 17). Applicant respectfully traverses this rejection.

The Office Action states:

> The cores of the '974 patent start out at 74 microns and are coated and sieved with a -10+60 mesh sieve, meaning that some particles sieved through the screen will have dimensions less than 2000 (-10 mesh) microns but the majority will be smaller and as small as 250 (60 mesh) microns. Of these particles it would have been obvious to sleek smaller particles since smaller particles would have an increased surface area when administered, increasing the total amount of pharmaceuticals administered to the patient.

As discussed above, the '974 patent teaches a pharmaceutical formulation quite different from the claimed pharmaceutical preparation. As acknowledged by the Examiner, "the core particles comprising a drug are coated to a sugar sphere." (Office Action, p. 4). This is the "immediate release particle." ('974 patent, col. 4, lines 12-20). "The immediate release particle core additionally contains an inert spherical substrate particle which aids in the diffusion/release of the drug from the formulation." (col. 5, lines 23-26). "The drug adheres to the inert spherical substrate particle through a binding agent which is preferably applied by a suitable solvent. (col. 5, lines 38-40).

The immediate release particle of the '974 patent, by definition, does not disclose the claimed sustained-release preparations. The '974 patent also does not disclose that the active pharmaceutical ingredient "forms a saturated solution within said coated microparticles after said administration," as presently claimed. Furthermore, the '974 patent does not disclose that the binder is "permeable to said active pharmaceutical ingredient," as presently claimed.

To obtain the extended release particles, the '974 patent coats the immediate release particles with a plasticizer and a film forming material as part of its dissolution modifying system. (col. 6, line 19 – col. 7, line 10). Thus, the extended release particles of the '974 patent comprise active pharmaceutical ingredient with a binder to adhere the active pharmaceutical ingredient to an inert spherical carrier that is then coated with a plasticizer and a film forming material. This is different from the presently claimed sustained-release preparations.

The '974 patent also discloses that its formulations are matrices. For example, the '974 patent states:

> In particular it is essential to use starting components of drug and inert carriers which have mesh sizes greater than 200 mesh. Such sizes aid in offering various advantages. First, they assist in making hard granules which improves the binding characteristics of the matrix.
>
> (col. 7, lines 30-35).

The '974 patent also states:

> By employing the formulations of the invention, one is able to achieve an extended release system which is a dynamic system composed of wetting, hydrating and dissolution components. At the same time, other soluble materials or drugs will also wet, dissolve and diffuse out of the matrix while insoluble materials will be held in place until the surrounding encapsulation layer erodes or dissolves away.
>
> (col. 7, lines 42-49).

The pharmaceutical preparation of the claims of the instant application are not a matrix, but comprise core particles comprising active pharmaceutical ingredient and a polymeric coating on those core particles. The difference between the claimed preparations and a matrix is described, for example, in the specification at ¶ [0054], which states, in pertinent part:

> [0054] If the active pharmaceutical ingredient and the first polymer-forming solution are both hydrophobic or hydrophilic, the core particle may partially or completely dissolve in the polymer-forming solution, resulting in microparticles in which the active pharmaceutical ingredient is interspersed or embedded in a matrix of the polymer as opposed to being coated by the polymer.

The specification describes the advantages of the present invention over the matrices formed in the prior art at ¶¶ [0059] and [0063], which read as follows:

> [0059] Moreover, many active pharmaceutical ingredients and many commonly-used polymer-forming solutions are hydrophobic in nature. As a result, core particles of such active pharmaceutical ingredients tend to dissolve in many commonly-used polymer-forming solutions if the solutions are applied directly, resulting in microparticles in which the active pharmaceutical ingredient is interspersed or embedded in a matrix of the polymer as opposed to being coated by the polymer. Depending upon the degree of dissolution, such microparticles may not exhibit pseudo-zero-order kinetics of release. Therefore, a first polymeric coating can be employed which is formed from a hydrophilic first polymer-forming solution in which the active pharmaceutical ingredient is substantially insoluble. A second polymeric coating formed from a hydrophobic second polymer-forming solution can then be employed without dissolving the active pharmaceutical ingredient. Conversely, for hydrophilic active pharmaceutical ingredients, a first polymeric coating can be formed from a hydrophobic first polymer-forming solution followed by a second polymeric coating formed from a hydrophilic second polymer-forming solution.
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> ...
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> [0063] In addition, in contrast to prior art sustained-release particle formulations, the core particles of the present invention constitute a substantially larger portion of the overall volume and weight of the coated microparticles and, conversely, the polymeric coating(s)

> constitute a substantially smaller portion. This is advantageous because the overall volume of microparticles which must be administered per unit weight of the active pharmaceutical ingredient is reduced relative to the prior art particles in which the active pharmaceutical ingredient is dissolved or interspersed in a relatively large volume and weight of polymeric matrix material which releases the active pharmaceutical ingredient as it degrades. This advantage arises from the different mechanism of action of the coated microparticles of the invention, in which a relatively thin polymeric coating can contain a relatively large core which contains a saturated solution of the active pharmaceutical ingredient and permits release by diffusion with pseudo-zero-order kinetics.

Thus, the pharmaceutical preparations of the claims of the instant application are not matrices.

In addition to requiring plasticizers and film forming materials, the '974 patent is also directed solely to pharmaceutical formulations for oral administration. When describing which drugs may be used in its formulations, the '974 patent states that a "wide variety of medicaments which are *orally administered* both in tablet, capsule and particulate form may be used to prepare particles according to this invention." (col. 4, lines 26-29) (*emphasis added*). The '974 patent also states that the "formulations of the invention are administered orally to mammals in suitable amounts to achieve the drug efficacy sought." (col. 9, lines 25-27). The '974 patent provides no teaching and makes no mention of parenteral administration.

Even if the '974 patent discloses particles from 250-2000 microns, as the Office Action contends, there is no teaching or suggestion in the '974 patent to formulate a pharmaceutical preparation for parenteral administration comprising microparticles that comprise core particles comprising an active pharmaceutical ingredient and a polymeric coating on those core particles, wherein the active pharmaceutical ingredient forms a saturated solution within the coated microparticles, wherein the polymeric coating is permeable to the active pharmaceutical ingredient, and wherein the particle sizes are as claimed in claims 6-8 and 31-33. Accordingly, a

person of skill in the art would not have understood or been motivated to modify the '974 patent to develop the claims of the instant application.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1, 6-8, and 31-33 under 35 U.S.C. § 103(a) based on the '974 patent be withdrawn.

B. U.S. Patent No. 5,271,946 to Hettche et al.

Claims 1, 21-23, and 48-50 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the '946 patent to Hettche.

An object of the '946 patent is to "provide a pharmaceutical composition containing the active substance azelastine which significantly reduces or completely eliminates the sedative effect of azelastine and which has a more acceptable taste." (col. 2, lines 13-17). The '946 patent achieves this object by providing pharmaceutical compositions for controlled release of azelastine. (col. 2, lines 20-22). However, these pharmaceutical compositions are very different from the claimed pharmaceutical preparations of the instant application. The '946 patent describes its compositions as follows:

> The composition contains conventional auxiliary substances and additives and a sustained release component which is characterized in that the active substance, azelastine, or its physiologically acceptable salts, are released in a controlled manner. A dosage unit of the composition contains 0.001 to 800 parts by weight of sustained release components are present together with each 1 part by weight of azelastine calculated as base.
>
> (col. 2, lines 22-30).

Thus, the compositions of the '946 patent are mixtures of "conventional auxiliary substances and additives and a sustained release component." The presently claimed preparation comprises core particles comprising the active pharmaceutical ingredient and a polymeric coating on those core particles. The core particles and polymeric coating are not simply mixed together.

The mixture of the '946 patent is further illustrated by the process for its preparation:

> The present invention also provides a process for the preparation of a drug formulation with controlled release of the active substance by incorporation of an active substance in conventional auxiliary and ancillary substances and a sustained release component which is characterized in that azelastine or its physiologically acceptable salts are used as the active substance to be released in a controlled manner in the ratio of 1 part by weight of azelastine, calculated as base, to 0.001 to 800 parts by weight of the sustained release component whereby the azelastine is released at a rate of 0.05 to 5 mg per hour.
>
> (col. 2, lines 42-54).

Thus, the "formulation with controlled release of the active substance" is a mixture of the "active substance in conventional auxiliary and ancillary substances" and "a sustained release component." The instantly claimed preparation is not a mixture and comprises a multiplicity of coated microparticles.

The '946 patent describes the coating of "active ingredient particles, granulate or pellet grains or azelastine-containing tablets." (col. 3, lines 63-65). The '946 patent makes no mention of coating of microparticles, as instantly claimed. The "particles" referred to are in the context of compositions such as pellet grains and tablets – compositions that are much larger than the instantly claimed microparticles. Furthermore, there is no teaching that the substances used to coat the active ingredient particles, granulate or pellet grains, or tablets must be permeable to the active ingredient, as presently claimed. Moreover, the '946 patent does not teach that the active pharmaceutical ingredient forms a saturated solution within the microparticles, as presently claimed.

The differences between the '946 patent and the claims of the instant application are further illustrated by the examples in the '946 patent. For example, Example 1 of the '946 patent describes preparation of the mixed formulation as follows:

> 100 g of azelastine hydrochloride are mixed with 960 g of hydroxypropyl methyl cellulose [viscosity of a 2% aqueous solution: 4000 cP (commercial product: e.g. Methocel K4M Premium)], 1320 g of spray-dried lactose and 20 g of magnesium stearate and the mixture pressed into tablets weighing 120 mg, having a diameter of 6 mm and a radius of curvature of 6 mm.
>
> In conjunction therewith the tablets may be provided in a conventional procedure with a gastric juice-soluble or gastric juice permeable or gastric juice-resistant film coating.
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> To produce a gastric juice-resistant coating, 1000 g of tablets are sprayed with about 1000 g of the following suspension, for example in a coating drum: ...
>
> (col. 12, lines 40-53).

The active pharmaceutical ingredient is mixed, not coated, with the sustained release component (i.e., hydroxypropyl methyl cellulose), as well as with other ingredients. Thus, the sustained release component does not form a permeable coating. The only coating that is provided in this Example is not added to cause the sustained-release of the active pharmaceutical ingredient, but to be either "gastric juice-soluble or gastric juice permeable or gastric juice-resistant." Such coatings relate to absorption of the active pharmaceutical ingredient in the stomach or the intestine, not to the sustained-release of a active pharmaceutical ingredient administered parenterally.

By mixing, rather than coating, the active pharmaceutical ingredient with a sustained release component, by failing to teach a polymeric coating that is permeable to the active pharmaceutical ingredient, and by failing to teach that the active pharmaceutical ingredient forms a saturated solution within the microparticle, the '946 patent does not teach the instantly claimed sustained-release preparations. This is illustrated in Example 9 of the '946 patent. As can be seen from the data in column 16, the release of the azelastine was highly non-linear. Such release does not even approximate the pseudo-zero-order release that can be obtained with the claimed preparations of the instant application.

The '946 patent was developed specifically to overcome the sedative effect and poor taste of azelastine. (col. 2, lines 13-17). There is no teaching or suggestion in the '946 patent that would allow a person of ordinary skill in the art to arrive at pharmaceutical preparations comprising microparticles that comprise core particles comprising an active pharmaceutical ingredient and a polymeric coating on those core particles, wherein the active pharmaceutical ingredient forms a saturated solution within the coated microparticles, wherein the polymeric coating is permeable to the active pharmaceutical ingredient, and wherein the weight of the polymeric coating is as claimed in claims 21-23 and 48-50.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1, 21-23 and 48-50 under 35 U.S.C. § 103(a) be withdrawn.

**CONCLUSION**

Applicant believes the rejections have been overcome and the claims are in condition for allowance. Applicant respectfully requests that a timely Notice of Allowance be issued.

The time for responding has been extended to March 25, 2010 by the accompanying Petition for Three-Month Extension of Time and payment of the fee. The Director is hereby authorized to charge Deposit Account No. 08-0219, under Order No. 0112924.00120US3, the amount of $555.00 for the three-month extension of time.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 08-0219, under Order No. 0112981.00125US36 from which the undersigned is authorized to draw.

Respectfully submitted,

Dated: March 25, 2010

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